REMARKS

Applicants have carefully studied the Office Action mailed on October 20, 2006, which issued in connection with the above-identified application. The present remarks are intended to be fully responsive to all points of rejection raised by the Examiner and are believed to place the claims in condition for allowance. Favorable reconsideration and allowance of the present claims are respectfully requested.

Applicants gratefully acknowledge the courtesy shown by Examiner Frederick Krass and the Examiner's Supervisor, Ardin Marschel, in discussing proposed amendments to the claims and other outstanding issues during a telephonic interview with applicants' representatives, Adda Gogoris, Tom Moran and Irina Vainberg, on December 19, 2006. Examiner's Interview Summary mailed on December 26, 2006 is attached as Exhibit A. The present response closely follows the Examiner's and Examiner's Supervisor's suggestions as specified in the Interview Summary.

Objections to the Specification

In the Office Action, the Examiner has objected to the specification due to lack of a statement as to its continuation status. An appropriate statement has been introduced in the above amendment to the specification.

Pending Claims

Claims 19-25 were pending and at issue in the application. In the Office Action, claims 19-25 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement and written description and under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 19-25 have been also provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 8 and 25 of the co-pending commonly owned continuation application No. 10/792,457.

Claim 25 has been canceled without prejudice or disclaimer.

Following the Examiner's and Examiner's supervisor's suggestions provided during the interview of December 19, 2006 (see Examiner's Interview Summary attached as Exhibit A), claim 19 has been amended to recite "an *aqueous* pharmaceutical formulation in the form of a nasal spray comprising an effective amount of an *analgesic comprising ketorolac, an optical isomer thereof, or a salt thereof* admixed with a bioadhesive polymer, said spray when administered to a human subject intranasally *will generate plasma levels of ketorolac in the subject within the range of 0.3-5 mg/liter of plasma*" (emphasis added). Support for this amendment can be found, for example, in the following parts of the specification:

1. "an aqueous pharmaceutical formulation in the form of a nasal spray" - p. 5, ll. 5-9; p. 6, l. 34 - p. 7, l. 7; Example 1;

2. "an analgesic comprising ketorolac, an optical isomer thereof, or a salt thereof" - p. 1, ll. 14-17; p. 1, l. 22 - p. 2, l. 3;

3. "said spray when administered to a human subject intranasally will generate plasma levels of ketorolac in the subject within the range of 0.3-5 mg/liter of plasma" - p. 4, l. 34 - p. 5, l. 4.

Dependent claim 20 has been amended to delete the term "ketorolac-based" to bring this claim in accordance with the amendment to claim 19.

New claims 26-31 have been added following the Examiner's and Examiner's Supervisor's suggestions provided during the interview of December 19, 2006 (see Examiner's Interview Summary attached as Exhibit A). These claims find support in the original claims and throughout the original specification. Specific support can be found, for example, in the following parts of the application:

1. "a pharmaceutical formulation in the form of a nasal spray comprising an effective amount of an analgesic comprising ketorolac, an optical isomer thereof, or a salt thereof" - p. 4, ll. 23-24; p. 6, ll. 1-3; p. 6, l. 34 - p. 7, l. 7; original claims 1 and 12 (*see* grandparent application Serial No. 07/875,700);

2. "an analgesic comprising ketorolac, an optical isomer thereof, or a salt thereof" - p. 1, ll. 14-17; p. 1, l. 22 - p. 2, l. 3; p. 3, ll. 15-27; original claims 1 and 12 (*see* grandparent application Serial No. 07/875,700);

3. "ketorolac, an optical isomer thereof, or a salt thereof admixed with a bioadhesive polymer" – p. 5, ll. 17-31; Example 3; original claim 8 (*see* grandparent application Serial No. 07/875,700);

4. "said spray when administered to a human subject intranasally forms a gel" - p. 5, ll. 17-31; Examples 3 and 6;

5. "said spray when administered to a human subject intranasally ... will generate plasma levels of ketorolac in the subject within the range of 0.3-5 mg/liter of plasma" - p. 4, l. 34 - p. 5, l. 4;

6. "ketorolac tromethamine" - p. 6, ll. 17-18; Examples 1-9 and 13-15;

7. "the analgesic is present in the composition in an amount of between 5 to 20% by weight based on total weight of the composition" - p. 4, ll. 19-21; Examples 1-9 (5%); Examples 13-15 (15%); original claims 4, 7 and 15-16 (*see* grandparent application Serial No. 07/875,700);

8. "the analgesic is present in the composition in an amount of 15% by weight based on total weight of the composition" - p. 4, ll. 19-21; Examples 13-15; original claims 7 and 16 (*see* grandparent application Serial No. 07/875,700);

9. ketorolac, an optical isomer thereof, or a salt thereof admixed with a bioadhesive polymer "selected from the group consisting of polyacrylics, cellulosics, and gums"- p. 5, ll. 17-31 (polyacrylics [also p. 7, ll. 8-20; Example 4], cellulosics [also p. 7, ll. 8-20; Examples 3, 6], gums, alginates, agar-agar); original claim 8 (*see* grandparent application Serial No. 07/875,700);

10. a pharmaceutical nasal spray "free of absorption enhancers" and containing "ketorolac, an optical isomer thereof, or a salt thereof admixed with a bioadhesive polymer" - Examples 3 and 6.

No new matter has been added as a result of these amendments, no new search is required and no new issues are raised. Following entry of these amendments, claims 19-24 and 26-31 will be pending.

Written Description Rejections

In the Office Action, claims 19-22 and 24 stand rejected under 35 U.S.C. §112, first paragraph, for lack of written description of the term "phospholipid" as used in claim 19.

Without addressing the merits of the rejection and in order to expedite the prosecution, the term "phospholipid" has been deleted thus rendering the rejection moot.

Claims 19 and 21-25 also stand rejected for lack of written description due to the use of the term "ketorolac-based analgesic" in claims 19 and 25.

As claim 25 has been canceled, the rejection of this claim is rendered moot.

Following the Examiner's suggestion, claim 19 has been amended to replace the term "ketorolac-based analgesic" with the phrase "analgesic comprising ketorolac, an optical isomer thereof, or a salt thereof". The term "ketorolac-based" has been also deleted in dependent claim 20.

In light of the above amendments, the written description rejections are believed to be overcome and withdrawal of such is kindly requested.

Enablement Rejection

Claims 19-25 have been also rejected under 35 U.S.C. §112, first paragraph, for lack of enablement of the phrase "ketorolac-based analgesic admixed with a bioadhesive polymer, said spray when administered intranasally having a therapeutic blood level comparable to that of the same formulation when injected". The Examiner contends that the specification, while being enabling for aqueous nasal sprays comprising ketorolac (and its optical isomers and salts) and a bioadhesive polymer selected from the group consisting of polyacrylics and carboxymethylcellulose, which when administered intranasally to mammals in amounts of 0.5-4 mg/kg/day will generate plasma levels of ketorolac of 0.3-5 mg/liter of plasma, does not reasonably provide enablement for such nasal sprays generally which "when administered intranasally" provide "a therapeutic blood level comparable to that of the same formulation when injected". The Examiner states that the present claims are unduly broad, because they encompass any type of solvent or bioadhesive and because, without specifying the relative drug concentrations, volumes administered, or the time periods at which the blood levels are measured, the functional limitation ("when administered intranasally" provide "a therapeutic blood level comparable to that of the same formulation when injected") is meaningless.

As claim 25 has been canceled, the rejection of this claim is rendered moot.

Following the Examiner's suggestions provided in the Office Action and during the telephonic interview of December 19, 2006 (see Examiner's Interview Summary attached as Exhibit A), claim 19 has been amended to recite "an *aqueous* pharmaceutical formulation in the form of a nasal spray comprising an effective amount of an analgesic comprising ketorolac, an optical isomer thereof, or a salt thereof admixed with a bioadhesive polymer, *said spray when administered to a human subject intranasally will generate plasma levels of ketorolac in the subject within the range of 0.3-5 mg/liter of plasma*" (emphasis added).

Also, following the Examiner's suggestions provided in the Office Action and during the telephonic interview of December 19, 2006 (see Examiner's Interview Summary attached as Exhibit A), new claim 26 has been added to recite "a pharmaceutical formulation in the form of a nasal spray comprising an effective amount of an analgesic comprising ketorolac, an optical isomer thereof, or a salt thereof admixed with a bioadhesive polymer, *said spray when administered to a human subject intranasally forms a gel and will generate plasma levels of ketorolac in the subject within the range of 0.3-5 mg/liter of plasma*" (emphasis added).

The above amendments are not to be construed as an admission of non-enablement of the rejected claims as they were made solely to expedite the prosecution.

Applicants respectfully submit that one skilled in the art would be able to practice the invention as recited in claim 19 as amended and new claim 26 without resorting to undue experimentation.

According to the current patent law and practice, there is no duty for the applicant to disclose each and every concentration and composition falling within the scope of the claims. Thus, Section 2164.03 of M.P.E.P. recites:

> the scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required (*In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir., 1991); *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971))

As further stated in section 2164.08 of M.P.E.P.:

> claims are not rejected as broader than the enabling disclosure under 35 U.S.C. 112 for non-inclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider them obvious (*In re Skrivan*, 427 F.2d 801, 806, 166 USPQ 85, 88 (CCPA 1970)). . . . When analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification.

See also *Application of Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976) (applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art"). Similarly, in *In re Rasmussen*, court stated that "a claim may be broader than the specific embodiment disclosed in a specification." 650 F.2d 1212, 1215, 211 USPQ 323, 326 (CCPA 1981). Finally, in *In re Goffe*, the court stated:

> To provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts. 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976).

As acknowledged by the Examiner and Examiner's Supervisor during the interview of December 19, 2006 (see Examiner's Interview Summary attached as Exhibit A), based on the aqueous nature of the spray and the specified plasma concentration of the drug recited in claim 19 as amended (or gel formation upon intranasal administration

and the specified plasma concentration recited in new claim 26), a person of ordinary skill in the art can easily select (using only routine experimentation) a proper bioadhesive polymer necessary to generate the requisite plasma level.

In fact, the present specification provides numerous specific examples of suitable bioadhesive polymers, including, e.g., hydroxypropyl cellulose (KLUCEL®), hydroxypropyl methyl cellulose (METHOCEL®), hydroxyethyl cellulose (NATROSOL®), sodium carboxymethyl cellulose (BLANOSE®), acrylic polymers (CARBOPOL®, POLYCARBOPHIL®), gum xanthan, gum tragacanth, alginates, and agar-agar (see, e.g., p. 5, ll. 17-31).

In light of the above amendments and remarks, the enablement rejections are believed to be overcome and withdrawal of such is kindly requested.

Indefiniteness Rejections

In the Office Action, claims 19-25 have been also rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Specifically, the Examiner objects to the use of the phrases "same formulation", "having a therapeutic blood level", and "ketorolac-based analgesic" in claims 19 and 25.

As claim 25 has been canceled, the rejection of this claim is rendered moot.

Following the Examiner's suggestions, claim 19 has been amended to replace (i) "same formulation" with "corresponding formulation", (ii) "having a therapeutic blood level" with "providing a therapeutic blood level", and (iii) "ketorolac-based analgesic" with "analgesic comprising ketorolac, an optical isomer thereof, or a salt thereof".

In light of the above amendments, the indefiniteness rejections are believed to be overcome and withdrawal of such is kindly requested.

Provisional Double Patenting Rejection

In the Office Action, claims 19-25 have been also provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 8 and 25 of the co-pending commonly owned continuation application No. 10/792,457 ('457 Application).

Without addressing the substantive distinctions with the present application, applicants respectfully note that a terminal disclaimer over the '457 Application should not be required in the present application, since it was filed before the '457 Application, and the '457 Application has not yet been allowed.

As stated in M.P.E.P. §804:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of ... two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. ... If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer.

In light of the above-presented arguments and M.P.E.P. §804, applicants respectfully request withdrawal of the double patenting rejection.

CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that claims 19-24 and 26-31 are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned agent at (212) 527-7634. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

Respectfully submitted,

Dated: January 18, 2007

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EXAMINER	
KRASS, FREDERICK F	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Interview Summary

Application No.	Applicant(s)	
09/903,665	SANTUS ET AL.	
Examiner	**Art Unit**	
Frederick Krass	1614	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Frederick Krass*.

(2) *Ardin Marschel (SPE 1614)*.

(3)*Irina Vainberg*.

(4)*Adda Gorgoris*

(5) Tom Moran.

Date of Interview: *19 December 2006*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *19*.

Identification of prior art discussed: *n/a*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *See Continuation Sheet*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments:

Applicant proposed amending claim 19 to read:

Claim 19 (Currently amended). A pharmaceutical formulation in the form of a nasal spray comprising an effective amount of an analgesic comprising ketorolac, and optical isomer thereof, or a salt thereof, admixed with a bioadhesive polymer, wherein said spray when administered to a subject intranasally will generate plasma levels of ketorolac in the subject within the range of 0.3-5mg/liter of plasma.

The examiner informed Applicant that the proposed amendment would be insufficient to obviate the 35 USC 112 rejections because 1) it failed to provide a frame of reference for administration (i.e., plasma levels could vary widely depending on the subject involved, e.g. if administered to a mouse versus an elephant and 2) no specific solvent or bioadhesive polymer was recited, whereas the art is highly unpredictable and component-specific.

The examiner indicated that the following additional amendments would be sufficient to obviate all grounds of rejection under 35 USC 112: 1) insert the word "human" before "subject" at the fourth line of the claim and 2) insert EITHER a) the term "aqueous" before "pharmaceutical" at the first line of the claim OR b) insert the term "forms a gel and" after "intranasally" at the fourth line of the claim. Examiner and Applicant agreed that change "1)" would suffice to provide a reasonable frame of reference for administration which one skilled in the art would readily appreciate in light of the teachings of the specification. Applicant stated that the language of change "2)" seemed plausible, but needed to consider further before actually adopting same.

Should Applicant ultimately agree to the changes suggested in subsection "2)", they will provide a detailed analysis of why one skilled in the art would be able to practice the invention as claimed without resorting to undue experimentation. (The basic reasoning is that the Stanley et al reference teaches that unpredictability resides in the solvent, and so when water is specified one can easily select a proper bioadhesive necessary to generate the requisite plasma level. Alternatively, when a gel is specified, the adhesiveness of the gel will provide sufficient residence time to generate same, regardless of the particular solvent employed).